Journal of Microbiology, Immunology and Infection (2014) 47, 15–22

Available online at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.e-jmii.com

ORIGINAL ARTICLE

Methicillin-resistant *Staphylococcus aureus* bacteremia in hemodialysis and nondialysis patients

Li-Ping Kan [a], Jung-Chung Lin [a], Sheng-Kang Chiu [a], Yen-Cheng Yeh [b], Te-Yu Lin [a], Ya-Sung Yang [a], Yung-Chih Wang [a], Ning-Chi Wang [a], Kuo-Ming Yeh [a,*], Feng-Yee Chang [a,c]

[a] *Division of Infectious Diseases and Tropical Medicine, Department of Internal Medicine, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan*
[b] *Department of Internal Medicine, Kaohsiung Armed Forces General Hospital, Kaohsiung, Taiwan*
[c] *Centers for Disease Control, Department of Health, Taipei, Taiwan*

Received 30 April 2012; received in revised form 31 July 2012; accepted 15 August 2012

KEYWORDS
Bacteremia;
Hemodialysis;
Methicillin-resistant *Staphylococcus aureus*;
Minimum inhibitory concentration

Background/Purpose: Increased mortality has been reported in patients treated with vancomycin for methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia with high minimum inhibitory concentration (MIC) values within the susceptibility range. However, this finding has not been verified in hemodialysis patients, who have much higher invasive MRSA infection rates than nondialysis patients. We aimed at comparing vancomycin MICs between hemodialysis and nondialysis patients, and identifying predictors of high vancomycin MICs and infection-related mortality in hemodialysis patients with MRSA bacteremia.
Methods: Patients with MRSA bacteremia from January 2008 through December 2009 were enrolled. Vancomycin MIC was determined for each first isolate using the Etest method. Clinical characteristics and vancomycin MICs were compared between hemodialysis and nondialysis patients. Factors associated with high vancomycin MIC (2 μg/mL) and infection-related mortality in hemodialysis patients were analyzed.
Results: A total of 162 MRSA bacteremia episodes were identified. Forty-four (27.0%) isolates were obtained from hemodialysis patients and 118 (73.0%) from nondialysis patients. Diabetes (63.3% vs. 39.8%, $p = 0.007$) and prior vancomycin exposure in 30 days (31.8% vs. 12.7%, $p = 0.005$) were more prevalent in hemodialysis group than in nondialysis group. A higher

* Corresponding author. Division of Infectious Diseases and Tropical Medicine, Department of Internal Medicine, Tri-Service General Hospital, National Defense Medical Center, No. 325 Cheng-Kung Road, Section 2, Nei-hu, Taipei 114, Taiwan.
E-mail address: kmyeh@ndmctsgh.edu.tw (K.-M. Yeh).

http://dx.doi.org/10.1016/j.jmii.2012.08.015

prevalence of vancomycin MIC of 2 μg/mL was observed in hemodialysis group in comparison with nondialysis group (11.4% vs. 1.7%, $p = 0.016$). In following analyses of hemodialysis group, patients with initial presentation of septic shock had a higher risk of vancomycin MIC of 2 μg/mL than nonseptic shock patients (100.0% vs. 38.5% $p = 0.014$). Infection-related mortality was associated with age, Acute Physiology and Chronic Health Evaluation II (APACHE-II) score >15, presence of septic shock, receipt of mechanical ventilation, and failure to remove source of bacteremia in univariate analysis.

Conclusion: Hemodialysis patients with MRSA bacteremia are more likely to have a high vancomycin MIC (2 μg/mL) compared with nondialysis patients. Infection-related mortality is associated with the patient's clinical manifestations, including age, APACHE-II score >15, presence of septic shock, receipt of mechanical ventilation, and failure to remove source of bacteremia. Treatment selection should be tailored according to the patient's clinical condition.

Introduction

Staphylococcus aureus is the most common pathogen of bloodstream infections (BSIs) in hemodialysis patients.[1,2] In 2005, invasive methicillin-resistant *S. aureus* (MRSA) infections occurred in 45.2/1000 dialysis patients, a rate more than 100 times higher than in nondialysis patients.[3] Patients with MRSA bacteremia who are undergoing hemodialysis have a five-fold higher risk for death and >100% higher hospital costs than uninfected patients undergoing hemodialysis.[4]

Vancomycin is one of the most commonly administered antimicrobial agents in hemodialysis patients, because of both high risk of systemic MRSA infections and ease of administration.[5] Despite its sustained *in vitro* microbiological inhibitory activities, emerging data suggest that vancomycin may be less effective against MRSA infections with minimum inhibitory concentrations (MICs) at the higher end of the susceptibility range.[6] Patients undergoing hemodialysis with MRSA bacteremia had been studied in the United States,[7] but no local data are available in Taiwan. We conducted this study to identify and compare the clinical characteristics and vancomycin MICs between hemodialysis and nondialysis patients with MRSA bacteremia. Factors associated with high vancomycin MIC and infection-related mortality in hemodialysis group were analyzed.

Materials and methods

Study design and patients

This retrospective study was conducted at Tri-Service General Hospital, a 1700-bed primary care and tertiary referral center in northern Taiwan. A list of patients with MRSA bacteremia from January 2008 through December 2009 was retrieved from the hospital's clinical microbiology laboratory database. The patients were divided into two groups. Hemodialysis group comprised all patients who had undergone hemodialysis for more than 3 months prior to enrollment; the remaining patients were classified as nondialysis group. Demographic data, comorbidities, Charlson Comorbidity Index, Acute Physiology and Chronic Health Evaluation II (APACHE-II) score, initial presentation of septic shock, surgery within 30 days, vancomycin exposure within 30 days, receipt of mechanical ventilation, use of vascular access device, vancomycin MICs, and infection-related mortality were retrospectively collected for all patients. Additionally, causes of hemodialysis, source of bacteremia, removal of source of bacteremia, administration of empirical antimicrobial agents, presence of persistent bacteremia, and mortality rate within 14 and 28 days after onset of bacteremia were analyzed in hemodialysis group.

Definition

MRSA bacteremia was defined as the presence of at least one set of blood culture yielding MRSA. Comorbidities were defined as diseases that cause functional impairment and/or predispose patients to infection, such as alcoholism (consumption of >100 g of alcohol per day), chronic obstructive pulmonary disease, dementia, diabetes, heart failure, hematological neoplasms, immunosuppressive therapy (>10 mg of prednisolone daily within 4 weeks, or other agents used as antineoplastic chemotherapy or to prevent organ rejection), liver cirrhosis, solid neoplasms, and valvular heart disease. Causes of hemodialysis were identified by either renal biopsy pathology report or medical record. Septic shock was diagnosed on the basis of standard clinical definition.[8] Hospital-onset BSI was defined as bacteremia occurring >48 hours after hospital admission. Surgery within 30 days was defined as operation under either general or local anesthesia in the past 30 days. All catheters used at onset of bacteremia were recorded. Tunneled catheters were passed under the skin from the insertion site to a separate exit site, where the catheter and its attachments emerge from underneath the skin (Por-A-Cath or double lumen catheter, for instance). Any dose of vancomycin exposure within 30 days was analyzed. Persistent bacteremia was defined as growth of MRSA with identical antibiogram on Day 7 or after, within 30 days of the first positive blood culture. Infection-related mortality was defined as death occurred (1) within 7 days after positive blood cultures or (2) prior to resolution of signs and symptoms of MRSA bacteremia or (3) 7 days after the onset of MRSA bacteremia without any obvious cause other than bacteremia.

Microbiologic methods

Only one MRSA isolate per patient was included in the microbiological portion of this study. All isolates were identified using routine bacteriological procedures. Methicillin susceptibility testing was performed using the disk diffusion method, in accordance with the criteria of the Clinical and Laboratory Standards Institute (CLSI).[9] Vancomycin MIC was determined using the Etest method, according to the manufacturer's guidelines. A suspension of saline calibrated to the 0.5-McFarland turbidity standard was plated onto Mueller—Hinton agar, onto which Etest strips (AB BIODISK, Solna, Sweden) were applied. The plates were incubated at 35°C for 24 hours. The MIC was interpreted as the zone of inhibition that corresponded to a concentration gradient on the Etest strips, according to the manufacturer's guidelines. Quality control was performed using the CLSI-recommended reference strain (ATCC 29213).[9]

Statistical analysis

Categorical variables were compared using χ^2 test or Fisher's exact test, and the Student *t* test was used for continuous variables. Multivariate logistic regression models were used to assess the predictors of vancomycin MIC of 2 μg/mL and the association with infection-related mortality. All analyses were performed using SPSS version 15.0 (SPSS Inc., Chicago, IL, USA).

Results

One hundred and sixty-two patients with MRSA bacteremia were included during January 2008 through December 2009, including 44 (27.0%) patients in hemodialysis and 118 (73.0%) patients in nondialysis group (Table 1). Patients with acute renal failure on temporary hemodialysis, or with end stage renal disease undergoing peritoneal dialysis were

Table 1 Demographics and clinical characteristics of 162 patients with methicillin-resistant *S. aureus* bacteremia

Variables	Hemodialysis, *n* = 44 (%)	Nondialysis, *n* = 118 (%)	*p*
Male sex	28 (63.6)	81(68.6)	0.546
Age (y, mean ± SD)	69.6 ± 15.6	69.1 ± 18.6	0.874
Comorbidity			
Alcoholism	1 (2.3)	8 (6.8)	0.446
Chronic obstructive pulmonary disease	7 (15.9)	17 (14.4)	0.811
Dementia	5 (11.4)	24 (20.3)	0.185
Diabetes	28 (63.3)	47 (39.8)	0.007
Heart failure	16 (36.4)	27 (22.9)	0.084
Hematologic neoplasm	1 (2.3)	11 (9.3)	0.183
Immunosuppressive therapy	8 (18.2)	27 (22.9)	0.518
Liver cirrhosis	2 (4.5)	10 (8.5)	0.515
Solid neoplasm	8 (18.2)	28 (23.7)	0.450
Valvular heart disease	10 (22.7)	13 (11.0)	0.058
Charlson Comorbidity Index >5	20 (45.5)	46 (39.0)	0.456
APACHE-II score >15	24 (54.5)	64 (54.2)	0.972
Septic shock	20 (45.5)	53 (44.9)	0.951
Hospital onset	23 (52.3)	78 (66.1)	0.106
Surgery within 30 d	28 (63.6)[a]	60 (50.8)[b]	0.146
Prior vancomycin exposure within 30 d	14 (31.8)	15 (12.7)	0.005
Receipt of mechanical ventilation	20 (45.5)	61 (51.7)	0.480
Vascular access device			
Tunneled catheter	14 (31.8)[c]	2 (1.7)[d]	<0.001
Nontunneled catheter	9 (20.5)[e]	64 (54.2)[f]	<0.001
Fistula or graft	21 (47.7)	0	—[g]
Vancomycin MIC			
MIC ≥1.5 μg/mL	22 (50.0)	57 (48.3)	0.848
MIC = 2 μg/mL	5 (11.4)	2 (1.7)	0.016
Infection-related mortality	18 (40.9)	49 (41.5)	0.944

APACHE-II = Acute Physiology and Chronic Health Evaluation II; MIC = minimum inhibitory concentration; SD = standard deviation.
[a] Six patients underwent debridements, 12 arteriovenous shunt surgeries, and 10 Hickman catheterizations.
[b] Twenty-four patients underwent debridements, 16 orthopedic surgeries, 10 abdominal surgeries, and 10 tracheostomies.
[c] Fourteen Hickman catheters.
[d] Two Port-A-Cath.
[e] Nine double-lumen catheters.
[f] Fifty-eight central venous catheters and six pulmonary artery catheters.
[g] Fistula or graft was not compared between hemodialysis and nondialysis patients because none of the nondialysis patients had fistula or graft.

not identified in our study. The median age was 69.3 years (range 20—97 years), and 67.2% patients were male. Clinical characteristics of the patients are shown in Table 1. Diabetes (63.3% vs. 39.8%, $p = 0.007$) and prior vancomycin exposure in 30 days (31.8% vs. 12.7%, $p = 0.005$) were more prevalent in hemodialysis group than in nondialysis group. Tunneled catheter use was more prevalent in hemodialysis group (31.8% vs. 1.7%, $p < 0.001$). All MRSA strains were susceptible to vancomycin (MICs $\geq$0.5 to $\leq$2 μg/mL). The prevalence of vancomycin MICs $\geq$1.5 μg/mL was similar in hemodialysis and nondialysis groups in this study (50.0% vs. 48.3%, $p = 0.848$). A higher prevalence of vancomycin MIC of 2 μg/mL was observed in hemodialysis group than in nondialysis group (11.4% vs. 1.7%, $p = 0.016$).

Infection-related and Day 28 mortality of hemodialysis and nondialysis patients with different vancomycin MICs are illustrated in Fig. 1. Infection-related mortality ranged between 42.1% and 60.0%, and Day 28 mortality between 40.0% and 50.0% in the two groups. No significant difference in infection-related and Day 28 mortality could be noted between hemodialysis and nondialysis groups regarding different vancomycin MICs.

Factors associated with high vancomycin MIC (2 μg/mL) in hemodialysis patients are analyzed in Table 2. In univariate analysis, septic shock was associated with a high vancomycin MIC of 2 μg/mL in hemodialysis group ($p = 0.014$, Table 2). No independent risk factor could be identified in the stepwise logistic regression, with heart failure, APACHE-II score >15, septic shock, and receipt of mechanical ventilation as variables. Other causes of hemodialysis in patients with vancomycin MIC <2 μg/mL included two drug-related nephropathy and four unknown causes. Other causes of MRSA bacteremia included one MRSA pneumonia in patients with a vancomycin MIC of 2 μg/mL, one MRSA pneumonia, and two primary bacteremia in patients with vancomycin MIC <2 μg/mL (Table 2). All hemodialysis patients with *S. aureus* bacteremia were empirically treated with vancomycin, while pending the antimicrobial susceptibility data. Time of initiation, dosage, and trough level of vancomycin are presented in Tables 2 and 3.

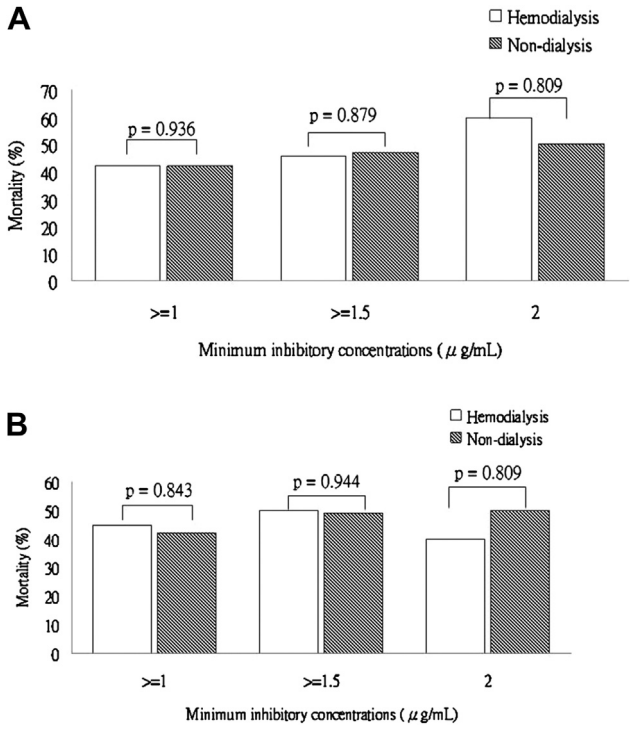

Figure 1. (A) Infection-related and (B) Day 28 mortality of hemodialysis and nondialysis patients with different vancomycin MICs. No significant difference could be noted between two groups regarding different minimum inhibitory concentrations.

Infection-related mortality in hemodialysis group in this study was 40.9% (Table 1). Univariate and multivariate analyses using infection-related mortality as a dependent variable were performed to identify factors associated with infection-related mortality in hemodialysis group (Table 3). In univariate analysis, age, APACHE-II score >15, presence of septic shock, receipt of mechanical ventilation, and failure to remove source of bacteremia were associated with infection-related mortality. In the stepwise logistic regression, no independent risk factor for infection-related mortality was identified.

Discussion

A higher prevalence of prior vancomycin exposure within 30 days in hemodialysis group than in nondialysis group was observed in this study. Widespread use of glycopeptides, especially vancomycin,[3] is known to be associated with the development of resistant organisms (vancomycin-resistant *Enterococcus* and *S. aureus)*.[10] Evaluation of the patient's clinical condition and prudent use of vancomycin are important due to the ever-changing bacterial resistance patterns.

A higher prevalence of vancomycin MIC of 2 μg/mL was observed in hemodialysis group in comparison with nondialysis group. Septic shock was associated with high vancomycin MIC (2 μg/mL) in hemodialysis group, although not an independent risk factor in this study. Several studies had been conducted to determine factors predicting high vancomycin MICs in patients with MRSA bacteremia. Patients with a history of prior vancomycin exposure within 30 days or infections in the intensive care unit (ICU) should be considered for high risk of strains with high vancomycin MICs ($\geq$1.5 μg/mL).[11] A clinical rule had been developed to predict a vancomycin MIC of 2 μg/mL, which included age >50 years, prior vancomycin exposure, history of MRSA bacteremia, chronic liver disease, and presence of a non-tunneled central venous catheter.[12] One case—control study performed in hemodialysis patients with MRSA bacteremia revealed that surgery within previous 6 months and ICU admission were significant risk factors for high vancomycin MIC (2 μg/mL). However, the role of prior vancomycin exposure was not evaluated in the study.[7]

We found that age, APACHE-II score >15, presence of septic shock, receipt of mechanical ventilation, and failure to remove source of bacteremia were associated with infection-related mortality in hemodialysis patients with MRSA bacteremia. Prognostic factors associated with mortality in general patients with MRSA bacteremia include complications, acute severe clinical condition at

Table 2 Factors associated with high vancomycin MIC (2 μg/mL) in 44 hemodialysis patients with methicillin-resistant *S. aureus* bacteremia

Variables	High MIC = 2 μg/mL $n = 5$ (%)	Low MIC <2 μg/mL $n = 39$ (%)	p
Male sex	5 (100.0)	23 (59.0)	0.141
Age (y, mean ± SD)	75.2 ± 9.4	68.9 ± 16.2	0.403
Comorbidity			
Alcoholism	0 (0.0)	1 (2.6)	1.000
Chronic obstructive pulmonary disease	0 (0.0)	7 (17.9)	0.574
Dementia	0 (0.0)	5 (12.8)	1.000
Diabetes	3 (60.0)	25 (64.1)	1.000
Heart failure	4 (80.0)	12 (30.8)	0.051
Hematologic neoplasm	1 (20.0)	0 (0.0)	0.114
Immunosuppressive therapy	2 (40.0)	6 (15.4)	0.219
Liver cirrhosis	1 (20.0)	1 (2.6)	0.217
Solid neoplasm	1 (20.0)	7 (17.9)	1.000
Valvular heart disease	1 (20.0)	9 (23.1)	1.000
Cause of hemodialysis			
Chronic glomerulonephritis	0 (0.0)	2 (5.1)	1.000
Cystic kidney disease	0 (0.0)	1 (2.6)	1.000
Diabetic nephropathy	2 (40.0)	17 (43.6)	1.000
Hypertensive nephropathy	3 (60.0)	12 (30.8)	0.319
Others	0 (0.0)	6 (15.4)	1.000
Source of bacteremia			
Skin and soft tissue	0 (0.0)	5 (12.8)	1.000
Bone and joint	1 (20.0)	1 (2.6)	0.217
Catheter related	2 (40.0)	21 (53.8)	0.658
Endocarditis or endovascular	1 (20.0)	11 (28.2)	1.000
Others	1 (20.0)	3 (7.7)	0.394
Charlson Comorbidity Index >5	4 (80.0)	16 (41.0)	0.160
APACHE-II score >15	5 (100.0)	19 (48.7)	0.053
Septic shock	5 (100.0)	15 (38.5)	0.014
Hospital onset	4 (80.0)	19 (48.7)	0.348
Surgery within 30 d	3 (60.0)	25 (64.1)	1.000
Prior vancomycin exposure within 30 d	2 (40.0)	12 (30.8)	0.647
Receipt of mechanical ventilation	4 (80.0)	16 (41.0)	0.160
Vascular access device			
Tunneled catheter	3 (60.0)	11 (28.2)	0.307
Nontunneled catheter	0 (0.0)	9 (23.1)	0.566
Fistula or graft	2 (40.0)	19 (48.7)	1.000
Failure to remove source of bacteremia	2 (40.0)	16 (41.0)	1.000
Time of bacteremia source removal (d, mean ± SD)	14.0 ± 10.8 ($n = 3$)	4.0 ± 4.3 ($n = 23$)	0.248
Vancomycin treatment			
Initiation within 24 h from bacteremia	4 (80.0)	22 (56.4)	0.634
1 g once per wk	3 (60.0)	15 (39.5)	0.634
1 g twice per wk	2 (40.0)	23 (60.5)	0.634
Vancomycin trough level (mean, μg/mL)	23.0 ± 12.0 ($n = 2$)	15.2 ± 7.4 ($n = 9$)	0.248
Persistent bacteremia	2 (40.0)	15 (40.5)	1.000
Infection-related mortality	3 (60.0)	15 (38.5)	0.386
Mortality within 14 d	1 (20.0)	12 (30.8)	1.000
Mortality within 28 d	2 (40.0)	14 (35.9)	1.000

Multivariate analysis was performed with heart failure, APACHE-II score >15, septic shock, and receipt of mechanical ventilation as variables, but failed to draw significance ($p > 0.05$). APACHE-II = Acute Physiology and Chronic Health Evaluation II; MIC = minimum inhibitory concentration; SD = standard deviation.

Table 3 Factors associated with infection-related mortality in 44 hemodialysis patients with methicillin-resistant *S. aureus* bacteremia

Variables	Infection-related mortality, $n = 18$ (%)	Survival, $n = 26$ (%)	p
Male sex	12 (66.7)	16(61.5)	0.728
Age (y, mean ± SD)	76.1 ± 8.3	65.2 ± 17.9	0.010
Vancomycin MIC			
MIC ≥ 1.5 μg/mL	10 (55.6)	12 (46.2)	0.540
MIC = 2 μg/mL	3 (16.7)	2 (7.7)	0.370
Comorbidity			
Alcoholism	1 (5.6)	0 (0.0)	0.409
Chronic obstructive pulmonary disease	3 (16.7)	4 (15.4)	1.000
Dementia	3 (16.7)	2 (7.7)	0.386
Diabetes	13 (72.2)	15 (57.7)	0.325
Heart failure	8 (44.4)	8 (30.8)	0.354
Hematologic neoplasm	0 (0.0)	1 (3.8)	1.000
Immunosuppressive therapy	4 (22.2)	4 (15.4)	0.697
Liver cirrhosis	1 (5.6)	1 (3.8)	1.000
Solid neoplasm	2 (11.1)	6 (23.1)	0.439
Valvular heart disease	5 (27.8)	5 (19.2)	0.716
Cause of hemodialysis			
Chronic glomerulonephritis	0 (0.0)	2 (7.7)	0.505
Cystic kidney disease	0 (0.0)	1 (3.8)	1.000
Diabetic nephropathy	10 (55.6)	9 (34.6)	0.168
Hypertensive nephropathy	6 (33.3)	9 (34.6)	0.930
Others	2 (11.1)	4 (15.4)	1.000
Source of bacteremia			
Skin and soft tissue	4 (22.2)	1 (3.8)	0.142
Bone and joint	1 (5.6)	1 (3.8)	1.000
Catheter related	5 (27.8)	18 (69.2)	0.007
Endocarditis or endovascular	5 (27.8)	7 (26.9)	1.000
Others	3 (16.7)	1 (3.8)	0.289
Charlson Comorbidity Index >5	9 (50.0)	11 (42.3)	0.614
APACHE-II score >15	18 (100.0)	6 (23.1)	<0.001
Septic shock	14 (77.8)	6 (23.1)	<0.001
Hospital onset	11 (61.1)	12 (46.2)	0.329
Surgery within 30 d	9 (50.0)	19 (73.1)	0.118
Prior vancomycin exposure within 30 d	6 (33.3)	8 (30.8)	0.858
Receipt of mechanical ventilation	13 (72.2)	7 (26.9)	0.003
Vascular access device			
Tunneled catheter	7 (38.9)	7 (26.9)	0.402
Nontunneled catheter	4 (22.2)	5 (19.2)	1.000
Fistula or graft	7 (38.9)	14 (53.8)	0.329
Failure to remove source of bacteremia	12 (66.7)	6 (23.1)	0.004
Time of bacteremia source removal (d, mean ± SD)	8.7 ± 8.9 ($n = 6$)	4.1 ± 4.6 ($n = 20$)	0.268
Vancomycin treatment			
Initiation within 24 h from bacteremia	9 (50.0)	17 (65.4)	0.307
1 g once per wk	8 (47.1)	10 (38.5)	0.576
1 g twice per wk	9 (52.9)	16 (61.5)	0.576
Vancomycin trough level (mean, μg/mL)	15.5 ± 10.1 ($n = 5$)	17.6 ± 7.2 ($n = 6$)	0.703
Persistent bacteremia	9 (52.9)	8 (32.0)	0.175

Multivariate analysis was performed with age, APACHE-II score >15, septic shock, receipt of mechanical ventilation, and failure to remove source of bacteremia as variables, but failed to draw significance ($p > 0.05$). APACHE-II = Acute Physiology and Chronic Health Evaluation II; MIC = minimum inhibitory concentration; SD = standard deviation.

onset, and inappropriate empiric treatment.[13] Several studies have suggested that age and MRSA nasal carriage are predictive of mortality in hemodialysis patients with MRSA bacteremia.[14,15] Li et al[14] suggested that age older than 65 years is independently associated with a higher risk of death in hemodialysis patients with *S. aureus* bacteremia. MRSA nasal carriers were found to have a 4.99-fold increased risk of infection-related mortality compared with noncarriers in an outpatient hemodialysis population.[15]

Failure to treat MRSA bacteremia with vancomycin MICs $\geq$1 μg/mL was first addressed by Sakoulas et al.[6] Subsequent studies showed a higher mortality rate in high vancomycin MIC group (MIC 2 μg/mL),[16–20] or treatment failure with vancomycin MICs $\geq$1[21] or $\geq$1.5 μg/mL.[11] Few studies have focused on the impact of high vancomycin MIC on hemodialysis patients with MRSA bacteremia. In our study, high vancomycin MIC (2 μg/mL) was not associated with infection-related mortality in hemodialysis group. In a case–control study performed among hemodialysis patients with MRSA bacteremia, patients with high vancomycin MIC (2 μg/mL) and low vancomycin MIC ($\leq$0.5 μg/mL) did not differ significantly with regard to mortality in multivariate analysis.[7]

According to the Infectious Diseases Society of America guideline for MRSA infections, for isolates with a vancomycin MIC of $\leq$2 μg/mL, the patient's clinical response should determine whether the use of vancomycin should be continued or not, independent of vancomycin MICs (A-III).[22] In a literature review by van Hal et al,[23] alternative anti-MRSA agents should be considered for MRSA BSIs with vancomycin MIC $\geq$2 μg/mL, as determined by Etest method, especially in patients with persistent disease.[23] There are very little data supporting better survival rates with alternative antibiotics for MRSA BSIs. One retrospective case–control trial showed better outcome with daptomycin than with vancomycin for the treatment of MRSA BSIs with vancomycin MICs of 1.5–2 μg/mL.[24] A study involving 470 MRSA isolates in Taiwan showed that isolates with vancomycin MIC of 2 μg/mL were all susceptible to linezolid and tigecycline, whereas most isolates (98.8%) were susceptible to daptomycin.[25] Future clinical trials for alternative anti-MRSA agents in high vancomycin MIC group are mandatory.

There are some limitations to this study. This study enrolled only patients from a single site. Institutional differences in patient populations, antibiotic prescribing patterns, and resistance patterns may affect its applicability to other institutions. Vancomycin exposure within 30 days may be biased due to retrospective nature of the study and possible missing record in other ambulatory hemodialysis clinics. The possibility of patient-to-patient transmission of high vancomycin MIC strains cannot be excluded due to lack of molecular studies to determine whether one or several clones are driving the observed results. MRSA carriage screening was not performed in our hemodialysis patients. The effect of concomitantly administered antibiotics should be a covariate in future analysis. The failure to identify predictors for high vancomycin MIC (2 μg/mL) and lack of association with infection-related mortality may be of less statistical power due to limited study number. Enrollment of more patients is mandatory in future clinical studies.

In conclusion, a higher prevalence of vancomycin MIC of 2 μg/mL was identified in hemodialysis group than in nondialysis group. More prevalent vancomycin exposure was observed in hemodialysis group. Although not being a significant risk factor for high vancomycin MIC, vancomycin should be used cautiously due to possible development of resistant organisms and potentially predictive of high vancomycin MICs as addressed by other studies.[11,12] Infection-related mortality is associated with the patient's clinical manifestations, including age, APACHE-II score >15, presence of septic shock, receipt of mechanical ventilation, and failure to remove source of bacteremia. Treatment selection should be tailored according to the patient's clinical condition.

Conflicts of interest

All contributing authors declare no conflicts of interest.

Acknowledgments

This study was supported by grants from the Tri-Service General Hospital, National Defense Medical Center (TSGH-C101-169,-117; MAB-101-1-1~4).

References

1. Collins AJ, Foley RN, Chavers B, Gilbertson D, Herzog C, Johansen K, et al. United States Renal Data System 2011 annual data report: atlas of chronic kidney disease & end-stage renal disease in the United States. *Am J Kidney Dis* 2012;**59**(1 Suppl. 1). A7, e1–420.
2. Koziol-Montewka M, Szczepanik A, Baranowicz I, Jozwiak L, Ksiazek A, Kaczor D. The investigation of *Staphylococcus aureus* and coagulase-negative staphylococci nasal carriage among patients undergoing haemodialysis. *Microbiol Res* 2006; **161**:281–7.
3. Centers for Disease Control. Invasive methicillin-resistant Staphylococcus aureus infections among dialysis patients—United States, 2005. *MMWR* 2007;**56**:197–9.
4. Reed SD, Friedman JY, Engemann JJ, Griffiths RI, Anstrom KJ, Kaye KS, et al. Costs and outcomes among hemodialysis-dependent patients with methicillin-resistant or methicillin-susceptible *Staphylococcus aureus* bacteremia. *Infect Control Hosp Epidemiol* 2005;**26**:175–83.
5. Moise PA, Smyth DS, El-Fawal N, Robinson DA, Holden PN, Forrest A, et al. Microbiological effects of prior vancomycin use in patients with methicillin-resistant *Staphylococcus aureus* bacteraemia. *J Antimicrob Chemother* 2008;**61**:85–90.
6. Sakoulas G, Moise-Broder PA, Schentag J, Forrest A, Moellering Jr RC, Eliopoulos GM. Relationship of vancomycin MIC and bactericidal activity to efficacy of vancomycin for treatment of methicillin-resistant *Staphylococcus aureus* bacteremia. *J Clin Microbiol* 2004;**42**:2398–402.
7. Maclayton DO, Suda KJ, Coval KA, York CB, Garey KW. Case–control study of the relationship between MRSA bacteremia with a vancomycin MIC of 2 microg/mL and risk factors, costs, and outcomes in inpatients undergoing hemodialysis. *Clin Ther* 2006;**28**:1208–16.
8. Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med* 2003;**31**:1250–6.
9. Clinical and Laboratory Standard Institute. *Methods for dilution antimicrobial susceptibility tests for bacteria that grow*

aerobically, M7eA6. Wayne, PA: Clinical and Laboratory Standard Institute; 2006.
10. Tokars JI, Miller ER, Stein G. New national surveillance system for hemodialysis-associated infections: initial results. *Am J Infect Control* 2002;**30**:288—95.
11. Lodise TP, Miller CD, Graves J, Evans A, Graffunder E, Helmecke M, et al. Predictors of high vancomycin MIC values among patients with methicillin-resistant *Staphylococcus aureus* bacteraemia. *J Antimicrob Chemother* 2008;**62**: 1138—41.
12. Lubin AS, Snydman DR, Ruthazer R, Bide P, Golan Y. Predicting high vancomycin minimum inhibitory concentration in methicillin-resistant *Staphylococcus aureus* bloodstream infections. *Clin Infect Dis* 2011;**52**:997—1002.
13. Gomez J, Garcia-Vazquez E, Banos R, Canteras M, Ruiz J, Baños V, et al. Predictors of mortality in patients with methicillin-resistant *Staphylococcus aureus* (MRSA) bacteraemia: the role of empiric antibiotic therapy. *Eur J Clin Microbiol Infect Dis* 2007;**26**:239—45.
14. Li Y, Friedman JY, O'Neal BF, et al. Outcomes of *Staphylococcus aureus* infection in hemodialysis-dependent patients. *Clin J Am Soc Nephrol* 2009;**4**:428—34.
15. Lai CF, Liao CH, Pai MF, Chu FY, Hsu SP, Chen HY, et al. Nasal carriage of methicillin-resistant *Staphylococcus aureus* is associated with higher all-cause mortality in hemodialysis patients. *Clin J Am Soc Nephrol* 2011;**6**:167—74.
16. Hidayat LK, Hsu DI, Quist R, Shriner KA, Wong-Beringer A. High-dose vancomycin therapy for methicillin-resistant *Staphylococcus aureus* infections: efficacy and toxicity. *Arch Intern Med* 2006;**166**:2138—44.
17. Soriano A, Marco F, Martinez JA, Pisos E, Almela M, Dimova VP, et al. Influence of vancomycin minimum inhibitory concentration on the treatment of methicillin-resistant *Staphylococcus aureus* bacteremia. *Clin Infect Dis* 2008;**46**:193—200.
18. Musta AC, Riederer K, Shemes S, Chase P, Jose J, Johnson LB, et al. Vancomycin MIC plus heteroresistance and outcome of methicillin-resistant *Staphylococcus aureus* bacteremia: trends over 11 years. *J Clin Microbiol* 2009;**47**:1640—4.
19. Wang J-L, Wang J-T, Sheng W-H, Chen Y-C, Chang S- C. Nosocomial methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia in Taiwan: mortality analyses and the impact of vancomycin, MIC = 2 mg/L, by the broth microdilution method. *BMC Infect Dis* 2010;**10**:159.
20. Crompton JA, North DS, Yoon M, Steenbergen JN, Lamp KC, Forrest GN. Outcomes with daptomycin in the treatment of *Staphylococcus aureus* infections with a range of vancomycin MICs. *J Antimicrob Chemother* 2010;**65**:1784—91.
21. Kullar R, Davis SL, Levine DP, Rybak MJ. Impact of vancomycin exposure on outcomes in patients with methicillin-resistant *Staphylococcus aureus* bacteremia: support for consensus guidelines suggested targets. *Clin Infect Dis* 2011; **52**:975—81.
22. Liu C, Bayer A, Cosgrove SE, Daum RS, Fridkin SK, Gorwitz RJ, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children: executive summary. *Clin Infect Dis* 2011;**52**:285—92.
23. van Hal SJ, Lodise TP, Paterson DL. The clinical significance of vancomycin minimum inhibitory concentration in *Staphylococcus aureus* infections: a systematic review and meta-analysis. *Clin Infect Dis* 2012;**54**:755—71.
24. Moore CL, Lu M, Cheema F, Osaki-Kiyan P, Perri MB, Donabedian S, et al. Prediction of failure in vancomycin-treated methicillin-resistant *Staphylococcus aureus* bloodstream infection: a clinically useful risk stratification tool. *Antimicrob Agents Chemother* 2011;**55**:4581—8.
25. Kao TM, Wang JT, Weng CM, Chen YC, Chang SC. *In vitro* activity of linezolid, tigecycline, and daptomycin on methicillin-resistant *Staphylococcus aureus* blood isolates from adult patients, 2006—2008: stratified analysis by vancomycin MIC. *J Microbiol Immunol Infect* 2011;**44**:346—51.